Chapter 1

Introduction
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Thyroid malignancies include those of follicular cell origin and those arising from the C cells. Cancers of follicular cell origin are by far the most common and include papillary, follicular Hurthle cell, poorly differentiated and anaplastic carcinoma. Of these subtypes, anaplastic is rare and is known for its extremely bad prognosis and almost universally fatal outcome. Similarly, poorly differentiated carcinomas also have aggressive behaviour and relatively unfavourable outcome. The three remaining subtypes, papillary, follicular and Hurthle cell are by far the most common, constituting over 90% of thyroid malignancies, with papillary (PTC) being the most common of the three. Unlike poorly differentiated and anaplastic thyroid cancers, these three subtypes are grouped as well differentiated thyroid cancers, and generally have excellent outcomes.

Although excellent outcomes are reassuring for patients and rewarding for treating clinicians, they present a problem for researchers. With less than 10% of patients expected to die of disease in 10 or more years, attempts to characterize disease outcomes, and the impact of interventions by prospective studies, would require huge patient numbers with prolonged follow up and therefore are recognized as not readily feasible [1].

There is widespread observation that the incidence of WDTC is rising, and that majority of the tumors and the patients in whom they arise have a favourable outcome. In terms of risk stratifying patients with WDTC, great steps have been made towards characterizing those patients at higher risk of recurrence and death. Treatment for WDTC is controversial, both in terms of surgical and adjuvant medical approaches. In the absence of randomized controlled trials, there have been two broad approaches to assessing different treatments; single institution reviews and multi institutional database reviews. Single institutional reviews have the strength of accurate surgical, pathological, treatment and outcome data, but are limited by patient number. Multi institutional database studies provide large numbers but lack accuracy in terms of treatment, histological analysis and disease specific follow up. The absence of level I evidence to guide treatment decisions have led to great controversy amongst clinicians responsible for managing WDTC. It is against this backdrop that we chose to study WDTC.

Increasing Incidence and Changing Trends in Well Differentiated Thyroid Cancer

Well differentiated thyroid cancer is the most common endocrine malignancy and is increasing in incidence across the world [2-14]. This increase is being seen particularly in papillary carcinoma [15]. The reasons for this increase are unclear and probably multi-factorial. Groups have suggested that increased exposure to ionizing radiation, either due to disasters such as Chernobyl or increased incidence due to routine medical surveillance, and imaging studies, [16] may play a role. The effect of changing trends in public health may have an effect, with both obesity [17, 18] and diabetes [19] being linked with a higher risk of thyroid cancer.

Not only are a greater number of cancers identified now in comparison with 4 decades ago, but the nature of the primary tumors detected has changed. Increased availability of diagnostic scanning, in particular high resolution ultrasound, has led to the discovery that high
rates of nodularity are detectable in the thyroid glands of otherwise normal individuals [20]. When discovered, needle biopsy of such nodularity may lead to detection of otherwise occult malignancies. Many investigators feel that this increased rate of detection is the major driver in the rising incidence of WDTC, and is contributing to the significant rise in incidence of small lesions [12]. The discovery of occult disease however may not be the only factor influencing the observed changes. A recent Surveillance, Epidemiology and End Results (SEER) Database review identified not only increases in micro carcinoma, but also in larger tumors over 4 and even over 6 cms, which would not be so easily explained by increased surveillance.

In addition to changes in the histological subtype, number and average size of WDTCs now detected, and the patient cohort in whom they present is also changing. Although rates are rising in all age groups, they are rising fastest in patients over the age of 45 years [21]. The impact of this change in average age remains to be seen. Women have been considered to have superior outcomes to men, however recent evidence suggests that the seemingly protective effect of gender may be lost after menopause [22].

Increasing incidence and changing patterns of both disease and patients affected by this disease, have led to great interest in WDTC and outcomes for patients who are diagnosed with this disease. Much attention has been paid to predicting outcome and the selection of appropriate therapy for these patients.

**Long Term Oncological Outcomes**

Work from the mid 20th century did much to outline the mode of death in patient with recurrent WDTC [23, 24] However, it was not until long term studies involving large patient cohorts were reported that an idea of disease biology became apparent.

The Lahey Clinic published its results in 1976, reporting mortality rates of 3% and 5% at 5 and 10 years respectively for a group of 441 patients treated for PTC [25]. Data from 576 patients treated within the US Airforce Hospitals [26, 27] suggested that with 10 years follow up only around 1% of patients would die of disease. Although rates of recurrence in this cohort were higher (15%), many of these recurrences were successfully salvaged. The Mayo Clinic experience of over 800 patients and up to 40 years follow up confirmed these findings. Less than 6% of patients in their cohort died of disease at 30 years and WDTC accounted for only 3% of overall mortality. Memorial Sloan Kettering Cancer Center reported their experience of 50 years and over 900 patients [28] with a survival of nearly 90%. Similarly promising results were published as the experience of a number of major US centers were reported throughout the 1980s and 1990s [29-32]. This US experience was reinforced by worldwide single institutional experiences, again reporting survival rates around 90% dependant on length of follow up [33, 34].

Methods of data collection in the United States including the National Cancer Database and SEER have allowed analysis of very large groups of patients treated for WDTC. In 2006 Davies et al. reviewed statistics in the SEER database and reported thyroid cancer mortality rates at 0.5 deaths per 100,000 population [12]. These rates had remained stable, despite the increase in incidence between 1973 and 2002. Similarly low rates have been reported by other groups who analyzed data at a national level [13, 35].
Evidence reflected the excellent outcomes that could be expected for patients with WDTC. However, not all patients did so well. Some patients would suffer disease recurrence despite adequate treatment, and would go on to die of disease, prompting investigators to analyze their experience in an attempt to devise methods to predict outcome on an individual patient basis.

**Development of Risk Prediction Systems**

With convincing long term evidence that most patients with WDTC have an excellent prognosis, balanced with clinical experience that some patients have more aggressive disease which leads to recurrence and death, several investigators turned their attention to predicting which patients might be expected to do badly. Although an increasing percentage of patients are now detected with limited local disease, some patients do present with advanced local, regional or distant disease. The impact of patient, tumor and treatment factors has been recognized to have an effect on both outcomes.

In the 1960s and 70s several reports in the literature confirmed that the cell type of origin for a thyroid cancer was crucial to outcome [36, 37]. For WDTC, in 1986 the Mayo Clinic group reported outcomes for 859 patients with papillary thyroid cancer (PTC) treated between the 1940s-1970s. Their results suggested that advanced age at diagnosis, extra thyroid extension and distant metastases were strong predictors of death. These results were replicated by a number of groups including Mazzaferri who reported on 576 patients with similar findings [26, 27]. Hay et al. from the Mayo Clinic combined the risk factors of age, tumor grade, extent of disease and size of primary lesion in to the “AGES” system for risk prediction. Stratifying patients this way allowed groups to be identified who were at low versus high risk of death. This was later refined to include completeness of surgical resection and reported as a “MACIS” score [38]. Cady et al. reviewed over 800 patients managed in the Lahey Clinic over 4 decades, and reported similar results, introducing the “AMES” system which included age, distant metastases, extra thyroid extension and size, again to stratify patients into high and low risk groups [30]. A similar group of risk factors was reported by Shah from Memorial Sloan Kettering Cancer Center [28] which gave rise to the “GAMES” system of stratification (including tumor grade on histology). They separated patients and tumors into high and low risk categories for death. They then used these 2 factors to classify cases as low, or high risk cases. They also introduced an intermediate risk group category for young patients with high risk tumor factors, and older patients with low risk tumor features. [39]. The impact of nodal metastases on mortality is limited and therefore has not been included in many of the major risk prediction systems. Early work by Cady et al. suggested that nodal metastases actually had a protective effect [40], a finding explained by the predominance of young patients in the cohort, and the association with young age and both excellent survival and higher rates of nodal metastases. Hughes et al. later showed that in patients under 45 years of age at presentation, regional metastasis was not associated with death. However, in older patient, regional disease had a significant impact on cause specific mortality [41]. The American Joint Committee on Cancer now includes N stage in stratification of patients over the age of 45 years [42].
Many similar risk prediction tools have been published, focusing on the risk of death from WDTC [43]. To this point, no system has demonstrated clear superiority. More recently, the American Thyroid Association (ATA) published guidelines for stratifying patients by risk of recurrence [44]. The factors involved once again included the presence of distant metastases, completeness of surgical resection and the presence of extra thyroid extension or adverse histological features. Unlike previously cited systems that predict death, nodal metastases are included as conferring an intermediate risk of recurrence. As almost no patients will die of WDTC, a system designed to predict recurrence rather than death may prove to be of more clinical utility to modern day clinicians.

With the ability to predict outcome for individual patients, clinicians were able to consider their therapeutic approach to patients with WDTC. The extent of primary surgery and the role of radioactive iodine (RAI) in the post operative management were scrutinized in an attempt to tailor therapy to both the disease and the patient.

**Evolution of the Surgical Management of Well Differentiated Thyroid Cancer – Primary Disease**

With improvements in understanding of the biology of WDTC came attempts to optimize treatment for the condition. Several investigators, looked at the results of different therapeutic approaches and analyzed their outcomes in search of the optimal trade off between improving outcome whilst preventing side effects.

Early opinions favouring conservative surgical therapy [45] were challenged by clinical series suggesting improved results for patients who underwent total thyroidectomy. Mazzaferri analyzed the outcomes of 576 patients treated in the US Airforce medical service [26], finding that patients who had total thyroidectomy had lower rates of cancer related death and recurrence than those patients who underwent less than thyroidectomy. The series was updated in 1994 to include 1355 patients treated both in the US Air force and Ohio State University Hospital. Again the authors demonstrated, on multivariate analysis, a link between more aggressive primary surgery and improved outcome. This experience seemingly provided strong data in support of total thyroidectomy for all but the smallest of tumors. However, this data should be viewed with the acknowledgment of significant limitations. The multi-institutional nature of the series introduced the potential for significant heterogeneity in treatment approaches across the centers. The surgeons involved in management were based at military hospitals, and may not have had the same rigorous surgical training and experience required of modern day thyroid surgeons. Seventeen percent of patients in that report underwent either less than lobectomy or subtotal thyroidectomy, both procedures which no longer have a place in the routine management of thyroid cancer [40]. The patients were not stratified by age, histology or extent of disease. Despite these limitations, this work provided an evidence base for increased application of total thyroidectomy in the management of WDTC.

In contrast to Mazzaferri’s work, Cady et al. reported the results of the Lahey Clinic in 1976 [40]. Seven hundred and ninety-two patients were operated in this single institution for WDTC. Their work suggested no improvement in survival resulting from excision of a seemingly uninvolved...
contralateral lobe. Hay and colleagues from the Mayo Clinic analyzed their outcomes in 860 patients with PTC. They found that for patients with low risk disease, total thyroidectomy did not result in improved outcomes when compared with lobectomy [46, 47]. A matched pair analysis of older patients with disease limited to the gland who underwent total thyroidectomy versus lobectomy at Memorial Sloan Kettering Cancer Center again demonstrated no advantage of more aggressive surgery, with the authors concluding that thyroid lobectomy should be used selectively in tumors less than 4cm in size, limited to the gland and without evidence of disease in the contralateral lobe [48].

The collection of data in resources such as the SEER database allowed analysis of large patient cohorts, which promised to resolve the debate on the required extent of surgical resection required. In 2007 Bilimoria et al reported outcomes for over 50000 patients recorded in the National Cancer Database (NCDB) [49]. They found that although total thyroidectomy did not affect outcome for patients with sub-centimeter disease, for all patients with primary lesions greater than 1cm, total thyroidectomy reduced recurrence and improved survival. This report was cited by the ATA, in their 2009 guidelines on the management of WDTC, which recommends that total thyroidectomy should be advised for all lesions over 1cm in size, and lobectomy reserved only for the smallest tumors in the absence of any other risk factors [44].

Although the Bilimoria study provided higher numbers than would ever have been achieved in any single institution series, significant limitations of the data are evident [50]. Detail on preoperative investigations relating to abnormalities in the contralateral lobe were not included. Completeness of surgical resection was not recorded, but is vital information, particularly when considering patients coded as with lobectomy, who would be inappropriately recorded if the contralateral lobe was found to be unresectable. No information on specific high risk histological subtypes of papillary carcinoma was included, and recurrence data was reported as locoregional, rather than separating local from nodal recurrence. Unlike single institutional series, which are able to report these important co-variables, these national level studies omit the critical data required to make the assumption that total thyroidectomy improves outcome. In contrast to the Bilimoria results, Haigh et al. used the additional data recorded in the SEER database to show that total thyroidectomy did not confer a survival advantage in either low or high risk groups using the AMES classification [51]. A similar multivariate analysis of the SEER database by Mendelsohn et al. controlling for tumor size in a cohort of over 20000 patients found no survival difference in patients who underwent total thyroidectomy rather than thyroid lobectomy [52]. Davies et al. reported similar results in an analysis of 35000 patients managed between 1973-2005, again finding no advantage in total thyroidectomy [53]. The National Thyroid Cancer Treatment Cooperative Study Group from North America reported on almost 3000 patients in 2006, and was unable to show an improved disease specific survival or disease free survival at any stage of disease based upon extent of surgery [54].

Debate over the extent of thyroid surgery required for WDTC relates in part to complications of total thyroidectomy versus lobectomy. Rates of complication for thyroid surgery are significant. A study of 5583 thyroid cases operated in the USA in 1996 for WDTC reported a post operative hypocalcemia rate of 10% and a recurrent laryngeal nerve palsy rate of around
Multi-center studies from Italy and Scandinavia reported very similar findings [56, 57]. Comparing total thyroidectomy with lobectomy, both US and Italian studies have reported higher rates of hypocalcaemia, unilateral vocal cord palsy and bilateral vocal cord palsy following total thyroidectomy rather than thyroid lobectomy performed for malignancy [56, 58]. Despite these results, which represent multi-institutional results, experts in thyroid surgery report very low rates of complication following either lobectomy or total thyroidectomy [59].

This contrast supports the observation that the risk of thyroid surgery is directly related to the operating surgeon's experience.

Despite conflicting evidence about both the oncological superiority of total thyroidectomy and the surgical complications that result from bilateral surgery, there has been a steady increase in the proportion of surgeries which are total thyroidectomy in the USA [60]. Total thyroidectomy is now the procedure of choice in around 90% of patients with WDTC 1cm or greater in the USA [61].

**Evolution of the Surgical Management of Well Differentiated Thyroid Cancer – Neck Dissection**

Whilst there is agreement that management of overt nodal metastases involves surgical resection of disease using a compartment orientated approach, the position in relation to management of the clinically N0 patient is highly controversial. Patients who have apparently intrathyroid disease enjoy excellent outcomes. Therefore, most groups have abandoned elective lateral neck dissection, as the significant potential morbidity outweighs any advantage in terms of recurrence or survival. Elective central neck dissection however, reveals nodal micrometastases up to 60% of cN0 cases [62]. This procedure can be performed safely in expert hands [63, 64] and leads to up-staging in patients over the age of 45 years [62-64]. The information gained from this additional dissection can be used to target patients for adjuvant radioactive iodine (RAI) or for administration of higher RAI doses in departments that use adjuvant RAI routinely [64]. Despite such arguments, elective central neck dissection has not been shown to improve survival or reduce recurrence rates.

In contrast to arguments in favour of elective central neck dissection, there is a lack of evidence that such additional surgery results in measurable benefit. No effect on outcome, either recurrence or survival has been demonstrated by individual studies [63, 64] or the meta analysis of results [65]. Sywak at al. demonstrated lower thyroglobulin in patients who underwent prophylactic neck dissection, however this effect lost significance with time [66]. For these reasons and a lack of evidence that such procedures can be performed in a community setting without increasing morbidity from nerve injury and hypocalcemia [57], routine elective neck dissection is not supported by most major international guidelines. The current American Thyroid Association Guidelines state “prophylactic central-compartment neck dissection may be performed in patients with papillary thyroid carcinoma, especially for advanced primary tumors (T3 or T4)” [44]. In addition, they recently considered the feasibility of performing a randomized controlled trial of elective central neck dissection, determining that over 5000 patients would have to be enrolled [1]. This conclusion means the question is unlikely ever to
be conclusively resolved, however it also highlights the fact that such elective surgery has such a small impact on outcome that surgeons must be sure that their rates of morbidity in relation to more aggressive surgery are sufficiently low to consider such a procedure.

The Role of Radioactive Iodine in the Management of Well Differentiated Thyroid Cancer

The role of RAI in the management of WDTC is also controversial. Recognition that RAI could be used to ablate normal thyroid tissue, and that it might have a tumoricidal effect on WDTC with seemingly low levels of side effects led to widespread use.

When Mazzaferri et al. considered the effect of RAI in their early work [26], they observed significant reductions in both recurrence and mortality in patients who received RAI. Their later work further supported the position that for patients with disease over 1.5cm, those treated with RAI had improved outcomes in comparison with those selected not to receive RAI. This observation led to a recommendation by the authors that RAI should be used in all tumors over 1.5cm in size. It should be noted, however, that the same limitations that were applied to interpretation of this group’s surgical findings should be borne in mind when considering their recommendations for RAI. A significant number of patients did not undergo true total thyroidectomy. Therefore significant volumes of thyroid tissue may have been left behind, limiting application of this groups conclusions in the modern era. The work from the Mayo clinic, analyzed in 2008, suggested that for 83% of their patients, no improvement in outcome was observed despite the increase in use of RAI throughout their 6 decade experience [67]. This group therefore recommends only using RAI routinely in patients deemed to be at high risk of recurrence or death from disease. A similar outcome was reported in a multi-institutional study of around 3000 patients from North America [54]. The authors observed no benefit in RAI for patients with low stage disease, but observed improved disease free survival and disease specific survival in patients considered high risk.

The American Thyroid Association included these studies in its guidelines, which currently recommend the routine use of RAI in only high risk patients, and do not support its use in the lowest risk patients (<1cm disease). For patients with intermediate risk disease (pT2 or N+) they recommend selective use based on the presence of any adverse risk factors such as previous radiation, or higher risk histologies.

Whilst the benefit of RAI in lower risk patients is questionable, the potential for salivary and lacrimal side effects, and post treatment dysphagia have been demonstrated by a number of groups. This treatment related morbidity has been shown to have a negative impact on quality of life [68-72]. In addition to morbidity, RAI has also been linked with increased rates of second primary malignancies [73, 74].

Despite conflicting evidence regarding efficacy, and growing evidence of the adverse effects of treatment, use of RAI has increased significantly in the USA [67]. It is perhaps not surprising, given the state of the evidence in relation to RAI, that there is wide variation in RAI use across the USA.
Aims and Brief Outline of this Thesis

With rates of WDTC having tripled in the US over the past 4 decades and similar trends being reported globally, the impact on international healthcare resources is significant and continues to grow. Over the past century, investigators have observed that the vast majority of patients with WDTC will not die of disease, and that with appropriate treatment, excellent outcomes can be achieved. Surgery is the mainstay of treatment, although disagreement exists over the extent of thyroidectomy.

In patients presenting with metastatic or large volume disease, or for patients with evidence of extra-thyroid extension, authors agree that total thyroidectomy is the primary procedure of choice. However, epidemiological studies of WDTC suggest that such high risk cases will provide only a minority of the workload in the future. Increasingly, we are seeing low volume disease presenting in an older patient group [21]. At least two thirds of patients seen in the US today have disease limited to the thyroid [2], the majority of which will measure 2cms or less (pT1). Outcomes in this group are excellent and therefore differences in treatment effects are likely to be small. The debate over management of such low risk patients is far from resolved. Prospective randomized trials of surgical therapy are unrealistic. Recruitment and follow up would be unachievable. In the absence of such high level evidence, clinicians have looked to single institution series and multi-institutional datasets for guidance. The main drawback of single institutional studies is low patient number, whereas multi-institutional studies lack the level of detailed data required to interpret the effect of different treatment regimens on outcome.

The role of RAI has also been debated, with similar concerns about the lack of high level evidence confounding a straightforward interpretation of the evidence presented. Although the routine use of RAI has been accepted for patients considered at high risk of death or recurrence, for the majority of patients, the position is less clear.

Despite (a) the increasing number of patients who present with early localized disease (b) the lack of convincing evidence that more aggressive surgery results in improved outcome in such patients (c) the lack of evidence that routine use of RAI in low risk patients is of benefit and (d) the known increase in side effects related to more aggressive surgical and medical treatment, an increasing percentage of patients are being managed with total thyroidectomy and post operative RAI. Inspite of this increasingly aggressive and potentially morbid treatment approach, no reduction in mortality rates has been observed over the past 2 decades. Memorial Sloan Kettering Cancer Center, in New York has a long tradition of thyroid cancer research. As one of the highest volume centers in the USA, the workload allows recruitment of a large patient cohort. Following previous analysis of records from 1930-1985, thyroid lobectomy is recommended in properly selected patients. A risk stratified approach to the use of RAI within our institution has also long been practiced, with RAI reserved mainly for use in high risk cases. This less aggressive approach to the management of WDTC sets our institutional practice apart from much of the world, and has given us the opportunity to update our experience with a contemporary group of patients, in regard to their outcomes.
and the effect of therapy on both recurrence and death.

In chapter 2 we compare our dataset with the previously reported cohort of patients from 1930-1985. We describe both the similarities and differences observed over 8 decades. In chapter 3 we report the mode of death now experienced in the few fatalities reported within our cohort. Chapter 4 focuses on the least aggressive oncologically sound procedure that should be considered for patients with WDTC, isthmusectomy. Chapter 5 describes the role of thyroid lobectomy in patients with disease limited to the gland, and chapter 6 extends this experience to patients considered localized, but with microscopic extra thyroid extension reported on the histopathology report. In chapter 7 we examine the outcomes of patients who had 0 nodes excised at their primary surgery (Nx), in an attempt to address the role of elective central neck surgery in such cases. Chapters 8 and 9 analyze the use of RAI in the management of WDTC, with a particular focus on those patients who can safely be considered for treatment without RAI.

The aim of this thesis is to provide evidence from a large, consecutive group of patients with WDTC managed in a single major institution, which has had a relatively stable approach to the surgery, pathological reporting, adjuvant therapy and post operative follow up over many years. We focus on outcomes for patients treated in a selective manner. We assess outcomes following less than total thyroidectomy. In patients treated with total thyroidectomy, we assess outcomes for patients selected not to receive RAI.
References
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Chapter 1 Introduction


